REMARKS

In view of the above amendments and the following remarks, reconsideration of the outstanding office action is respectfully traversed. Pursuant to 37 CFR § 1.21, attached as an Appendix is a Version With Markings to Show Changes Made.

The January 18, 2002, personal interview between Examiners Prouty and Hutson, applicant Steven Goldman, M.D., Ph.D., and applicants' undersigned attorney is gratefully acknowledged. The substance of that interview is summarized below.

The rejection of claims 17 and 18 under 35 U.S.C. § 102(b) as anticipated by Armstrong, et. al., "Pre-Oligodendrocytes from Adult Human CNS," J. Neurosci. 12(4): 1538-47 (1992) ("Armstrong") is respectfully traversed in view of the cancellation of these claims.

The rejection of claims 17-20 under 35 U.S.C. § 102(b) over Kirschenbaum, et. al., "*In Vitro* Neuronal Production and Differentiation by Precuror Cells Derived from the Adult Human Forebrain," Cerebral Cortex 6: 576-89 (1994) ("Kirschenbaum") is respectfully traversed.

The study described in Kirschenbaum was carried out in the laboratory of applicant Steven A. Goldman, M.D., Ph.D. who was the supervising scientist on the study and, therefore, this work is fully understood by Dr. Goldman (See accompanying Declaration of Steven A. Goldman under 37 C.F.R. § 1.132 ("Goldman Declaration") ¶ 5). Kirschenbaum cultures samples of adult temporal lobes under conditions suitable for neuronal differentiation, while exposed to ^{3}H-thymidine (Id.). These samples were incubated for 7-28 days, stained for neuronal and glial antigens, and autoradiographed (Id.). Neuron-like cells were found in explant outgrowths and monolayer dissociates of the subependymal zone and periventricular white matter but not the cortex (Id.). A small number of Map-2^{+} and Map-5^{+}/glial fibrillary acidic protein^{-} cells did incorporate ^{3}H-thymidine, suggesting neuronal production from precursor mitosis (Id.). However, the O4^{+} oligondendrocytes were postmitotic (Id.). Even though the abstract of Kirschenbaum states that "O4^{+} oligodendrocytes, although the predominant cell type, were *largely* postmitotic (emphasis added)", Dr. Goldman only said this, because he is reluctant to make conclusions in absolute terms (Id.). Nevertheless, it is clear from the following statement on page 582 of Kirschenbaum that, in fact, *all* of the oligodendrocytes were post-mitotic:

> These $O4^+/GFAP^\pm$ cells were mitotically quiescent; among a sample of 8044 such cells, culled from four plates of subcortical white matter (2011 ± 858.6 $O4^+$ cells/plate, mean ± SD), *none* incorporated ^{3}H-thymidine *in vitro*, despite the frequent observation of ^{3}H-thymidine-labeled astrocytes in the same plates (emphasis in original).

(Id.). The failure of the Kirschenbaum study to identify mitotic oligodendrocyte progenitor cells caused Dr. Goldman to continue working to identify and produce such cells which efforts were ultimately successful in producing the invention of the present application (Id.). Since Kirschenbaum does not disclose mitotic oligodendrocyte progenitor cells or oligodendrocytes generated from such progenitors as claimed, the rejection based on this reference should be withdrawn.

The rejection of claims 17 and 19 under 35 U.S.C. § 102(b) as anticipated by U.S. Patent No. 5,276,145 to Bottenstein ("Bottenstein").

Bottenstein is directed to substantially purified preparations containing a neural progenitor regulatory factor that is important in regulating and coordinating production of oligodendrocytes and type 2 astrocytes (Goldman Declaration ¶ 6). The identification and purification of this factor was carried out with brain cells derived from neonatal rats of 1-3 days of age. These cells represented a mixture of cell types that included "progenitors", "Type 2 Astrocytes", "Early Oligodendrocytes", "Late Oligodendrocytes", "Total Oligodendrocytes", "Type 1 Astrocytes", and "Microglia" (Id.).

There are fundamental differences between the biology of rat and human oligodendrocyte progenitor cells (Goldman Declaration ¶ 7). These are unaddressed in Bottenstein, which discusses findings limited to neonatal rat brain (Id.). Whereas rat oligodendrocytes appear to retain mitotic potential, human oligodendrocytes do not (see Kirschenbaum) (Id.). As a result, the oligodendrocyte progenitor cell of the rat brain cannot be considered homologous to its human counterpart (Id.). In particular, methods that permit the selective extraction and/or growth of oligodendrocyte progenitors from the rat brain do not differentiate between oligodendrocyte progenitor cells and mature oligodendrocytes able to re-enter the mitotic cycle (Id.). In humans, these constitute two discrete phenotypes, lineally related but temporally distinct (Id.). The present invention teaches the selective acquisition of a highly enriched – to virtual purity - mitotically-competent oligodendrocyte progenitor cell pool, operationally separate and distinct from post-mitotic or mature oligodendrocytes (Id.).

Bottenstein was directed at the enrichment of glial progenitor cells from newborn rat brain (Goldman Declaration ¶ 8). Newborns have an abundant population of still-developing oligodendrocyte progenitor cells that may constitute a significant fraction of all of the cells in

neonatal brain tissue (Id.). Bottenstein reported that >30% of the cells of its tissue dissociates expressed the marker of this phenotype (Id.). With the addition of B104 conditioned media and the neural progenitor regulatory factor, this fraction increased to just over 40% (Id.). The nature of these cells is that of a still-mixed pool, in that the following populations appear to be represented by Bottenstein's data: astrocytes, oligodendrocytes, and a mixture of oligodendrodendroglial lineage cells of widely different developmental stages (Id.).

In contrast to the cells acquired from newborn rats using the Bottenstein protocol, the present invention is achieved with a procedure that permits, in both young and old humans, the selective extraction of progenitor cells strongly biased to oligodendrocytic phenotype, and allows the purification of these cells, including those from tissues in which they are scarce (e.g., postnatal and adult brain tissues harboring <1% of the desired oligodendrocyte progenitor cell type) (Goldman Declaration ¶9.). In Example 5 of the present patent application, the virtual purification of oligodendrocyte progenitor cells from tissues with a P/CNP2 promoter-targeted FACS-defined incidence of <1% was reported (Id.). This constituted a far greater enrichment of the oligodendrocyte progenitor cell (i.e. 170-fold) than that achieved by Bottenstein (i.e. less than 1.5-fold) and yields a far more pure product of oligodendrocyte progenitor cells (Id.).

In contrast to Bottenstein, the human oligodendrocyte progenitor cell populations achieved through the protocols of the present invention are virtually pure as to phenotype (Goldman Declaration ¶ 10). Compare Figure 5B to its control, Figure 5A (Id.). In Figure 5A, the gated single cell represents the false-positive sort incidence (Id.). Such incidences constitute <1% of the frequency of events noted in Figure 5B, indicating >99% purity of the P/CNP2:hGFP-sorted oligodendrocyte progenitor cells (Id.). This can be modulated as a function of sort speed to achieve any desired degree of purity, the trade-off being lower yields as higher degrees of purification are achieved (Id.). By virtue of the high-purity extraction attainable by fluorescence-activated cell sorting, the progenitor cells produced according to the present invention are never exposed to paracrine factors released by other cells, after removal from tissue (Id.). This permits their maintenance in an undifferentiated and phenotypically-unbiased state, in contrast to the mixed cellular milieu afforded by Bottenstein, in which non-oligodendrocytic and non-glial progenitor-derived phenotypes remain abundant (Id.).

As a result of these considerations, the selective propagation of mitotically-active oligodendrocyte progenitor cells from the neonatal rat brain, as taught by Bottenstein, does not predict the successful isolation of mitotic oligodendrocyte progenitor cells from postnatal or adult human brain tissue (Goldman Declaration ¶ 11). For all of these reasons, the rejection of claims 17 and 19 under 35 U.S.C. § 102(b) as anticipated by Bottenstein should be withdrawn.

The rejection of claims 18 and 20 under 35 U.S.C. § 103 for obviousness over Bottenstein is respectfully traversed for substantially the reasons noted above. As further evidence of the non-obviousness of the present invention, applicants hereby submit the June 7, 2000, Research/Clinical Update for the National Multiple Sclerosis Society (attached hereto as Appendix 1) which states:

> Researchers at Cornell University Medical College, supported by the National MS Society, have for the first time isolated cells in the adult human brain that can divide and grow into myelin-making cells and that may ultimately be capable of replacing those damaged in multiple sclerosis.

For all the reasons noted above, the rejection of claims 18 and 20 under 35 U.S.C. § 103 for obviousness over Bottenstein should be withdrawn.

In view of all the foregoing, it is submitted that this case is in condition for allowance and such allowance is earnestly solicited.

Respectfully submitted,

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Appendix A

Version With Markings to Show Changes Made

In reference to the amendments made herein to claim 19, additions appear as underlined text, while deletions appear as bracketed text, as indicated below:

In the Claims:

19. (Twice Amended) An enriched or purified preparation of human mitotic oligodendrocyte progenitor cells.

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RESEARCH/CLINICAL UPDATE

January 7, 2000

RESEARCHERS FIND KEY CELLS IN ADULT BRAIN THAT MAY SOMEDAY REPAIR MYELIN IN MS

Summary:

- Researchers at Cornell University Medical College, supported by the National MS Society, have for the first time isolated cells in the adult human brain that can divide and grow into myelin-making cells and that may ultimately be capable of replacing those damaged in multiple sclerosis.
- Although very basic in nature, this research may eventually lead to therapies for MS either through implantation of such cells, or through development of ways of stimulating progenitor cells resident in a person's brain to produce new oligodendrocytes that can repair myelin damaged by MS and possibly restore nerve function.

Details: National MS Society-supported investigators led by Steven A. Goldman, MD, PhD, of Cornell University Medical College, have reported the discovery and isolation of a population of immature ("progenitor") myelin-making cells (oligodendrocytes) in the brains of adult humans. These cells have the potential to repair myelin that has been destroyed by MS, and possibly to aid in the recovery of function.

Reporting in the November 15 issue of *The Journal of Neuroscience*, the investigators describe having found that the oligodendrocyte progenitor cells are surprisingly abundant in adult brain matter, and are capable of dividing to produce new oligodendrocytes. Most adult human brain cells do not divide. This is the first demonstration that such cells can be stimulated to divide and give rise to new oligodendrocytes.

Background

Throughout the 1990s, researchers had been searching for oligodendrocyte progenitor cells in the human brain. Oligodendrocyte progenitor cells had been found in the rat brain in the 1970s and 1980s. Immature oligodendrocytes had been found in human

brain tissue, but none of these had been capable of dividing. Researchers had begun to conclude that oligodendrocyte progenitor cells capable of dividing did not exist in the adult human brain. But by using surgically removed samples of adult human brain tissue, combined with newly developed techniques of molecular cell identification and separation, Goldman and colleagues were able to refute this notion and for the first time, segregate a population of dividing oligodendrocyte progenitors in adult brain.

The study

In this study, reported in the November 15 issue of *The Journal of Neuroscience*, adult human brain cells were obtained from brain matter that was removed from eight patients ranging in age from 24 to 65 years old, who underwent surgery for a variety of disorders. The investigators used a technique they had developed and tested in animal brain cells to separate living progenitor cells from the larger brain cell population.

The investigators identified a discrete population of oligodendrocyte progenitor cells, which they estimated to represent about four percent of the population of cells in the in the white matter of the brain. They then segregated the progenitor cells, and demonstrated that they were capable of dividing, "more or less on demand," says Goldman.

What the Study Means

This study shows that oligodendrocyte progenitor cells exist within the adult human brain and are capable of dividing. Furthermore, this study describes a method for the isolation and actual purification of these cells, potentially in large numbers. This raises the possibility that patients with MS might someday be treated either by transplanting oligodendrocyte progenitor cells, or by stimulating the patients' own oligodendrocyte progenitor cells to divide and produce new cells. Treatments might also be devised that combine elements of both approaches.

Dr. Goldman's team is currently conducting studies to determine whether transplanted oligodendrocyte progenitor cells will be able to produce replacement myelin on nerve fibers whose myelin has been destroyed. Studies will also be needed to determine whether stimulating the growth of new oligodendrocytes from progenitor cells that exist within a patient's brain will remyelinate damaged neurons.

The National MS Society is actively funding these and other efforts to find ways to repair myelin and nerve cells that have been destroyed by multiple sclerosis, with the hope of restoring nerve function.

From: Research Programs Department